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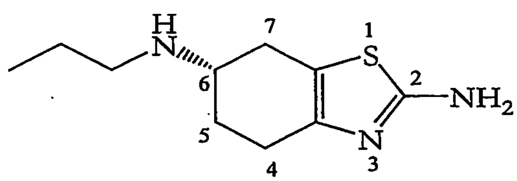
PROCESS FOR THE PREPARATION OF 2-AMINO-4,5,6,7-TETRAHYDRO-6-AMINOBENZOTHIAZOLES FROM CYCLOHEXANES AND CYCLOHEXANONES AS INTERMEDIATES

Technical field

The present invention relates to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles and to novel cyclohexanes and cyclohexanones for use in these processes.

Background art

Certain 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are known to have dopamine D-2 activity and are therefore potentially useful as pharmaceuticals for the treatment of psychiatric disorders such as schizophrenia and Alzheimer's disease. One such compound, the dihydrochloride salt of (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole **I** (pramipexole), is marketed as a pharmaceutical for the treatment of Parkinson's disease. The numbering of pramipexole **I** is indicated below.



I

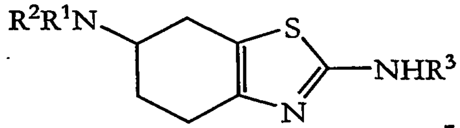
Processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are disclosed in patents US 4843086, US 4886812 and patent applications WO 02/22590 A1 and WO 02/22591 A1. A procedure to these types of compound is also disclosed by C.S. Schneider and J. Mierau in J. Med. Chem., 1987, vol. 30, pages 494-498.

However, known processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are not satisfactory, particularly for industrial scale manufacture, as they have been found to be low yielding and involve the use of

hazardous and difficult to handle reagents such as bromine, hydrazine and potassium chromate.

Summary of the invention

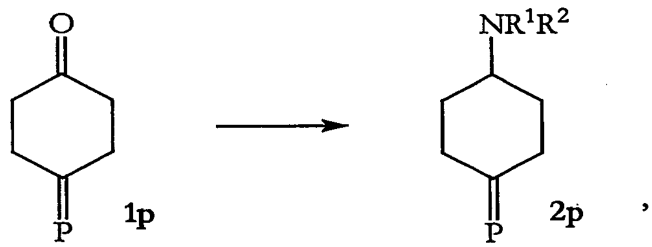
A first aspect of the present invention is a process for the preparation of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a**



5a

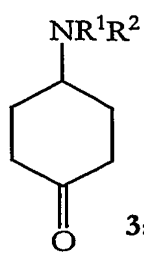
or a salt thereof, comprising the steps of:

(a) reductively aminating a protected cyclohexandione **1p** with an amine R^1R^2NH to yield a protected 4-amino-cyclohexanone **2p**:



wherein P is a protected ketone functionality, and R^1 and R^2 are any atom or group or, together with the nitrogen to which they are attached, form a ring;

(b) deprotecting the protected 4-amino-cyclohexanone **2p** to yield an unprotected 4-amino-cyclohexanone **3a**



3a ; and

(c) treating the unprotected 4-amino-cyclohexanone **3a** with iodine and a substituted thiourea $H_2N(C{=}S)NHR^3$, wherein R^3 is any atom or group, to yield the 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof.

For the purposes of the present invention, an "alkyl" group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkyl groups are methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups. Preferably an alkyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkyl group is a C_1-C_{12} alkyl group, which is defined as an alkyl group containing from 1 to 12 carbon atoms. More preferably an alkyl group is a C_1-C_6 alkyl group, which is defined as an alkyl group containing from 1 to 6 carbon atoms. An "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon double bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkenyl groups are vinyl, allyl, but-1-enyl and but-2-enyl groups. Preferably an alkenyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkenyl group is a C_2-C_{12} alkenyl group, which is defined as an alkenyl group containing from 2 to 12 carbon atoms. More preferably an alkenyl group is a C_2-C_6 alkenyl group, which is defined as an alkenyl group containing from 2 to 6 carbon atoms. An "alkenylene" group is similarly defined as a divalent alkenyl group.

An "alkynyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon triple bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkynyl groups are ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups. Preferably an alkynyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkynyl group is a C_2-C_{12} alkynyl group, which is defined as an alkynyl group containing from 2 to 12 carbon atoms. More preferably an alkynyl group is a C_2-C_6 alkynyl group, which is defined as an alkynyl group containing from 2 to 6 carbon atoms. An "alkynylene" group is similarly defined as a divalent alkynyl group.

An "aryl" group is defined as a monovalent aromatic hydrocarbon. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably

an aryl group does not include any heteroatoms in its carbon skeleton. Preferably an aryl group is a C_4-C_{14} aryl group, which is defined as an aryl group containing from 4 to 14 carbon atoms. More preferably an aryl group is a C_6-C_{10} aryl group, which is defined as an aryl group containing from 6 to 10 carbon atoms. An "arylene" group is similarly defined as a divalent aryl group.

Where a combination of groups is referred to as one moiety, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule. A typical example of an arylalkyl group is benzyl.

For the purposes of this invention, an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group may be substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-R^4$-O-R^5, $-R^4$-S-R^5, $-R^4$-SO-R^5, $-R^4$-SO_2-R^5, $-R^4$-SO_2-OR^5, $-R^4$O-SO_2-R^5, $-R^4$-SO_2-N$(R^5)_2$, $-R^4$-NR^5-SO_2-R^5, $-R^4$O-SO_2-OR^5, $-R^4$O-SO_2-N$(R^5)_2$, $-R^4$-NR^5-SO_2-OR^5, $-R^4$-NR^5-SO_2-N$(R^5)_2$, $-R^4$-N$(R^5)_2$, $-R^4$-N$(R^5)_3^+$, $-R^4$-P$(R^5)_2$, $-R^4$-Si$(R^5)_3$, $-R^4$-CO-R^5, $-R^4$-CO-OR^5, $-R^4$O-CO-R^5, $-R^4$-CO-N$(R^5)_2$, $-R^4$-NR^5-CO-R^5, $-R^4$O-CO-OR^5, $-R^4$O-CO-N$(R^5)_2$, $-R^4$-NR^5-CO-OR^5, $-R^4$-NR^5-CO-N$(R^5)_2$, $-R^4$-CS-R^5, $-R^4$-CS-OR^5, $-R^4$O-CS-R^5, $-R^4$-CS-N$(R^5)_2$, $-R^4$-NR^5-CS-R^5, $-R^4$O-CS-OR^5, $-R^4$O-CS-N$(R^5)_2$, $-R^4$-NR^5-CS-OR^5, $-R^4$-NR^5-CS-N$(R^5)_2$ or $-R^5$. In this context, $-R^4-$ is independently a chemical bond, a C_1-C_{10} alkylene, C_1-C_{10} alkenylene or C_1-C_{10} alkynylene group. $-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl. Optional substituent(s) are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituent(s).

Any optional substituent may be protected. Suitable protecting groups for protecting optional substituents are known in the art, for example from "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

For the purposes of this invention, a "salt" is any acid addition salt, preferably a pharmaceutically acceptable acid addition salt, including but not limited to a hydrohalogenic acid salt such as hydrofluoric, hydrochloric, hydrobromic and hydroiodic acid salt; an inorganic acid salt such as nitric, perchloric, sulfuric and phosphoric acid salt; an organic acid salt such as a sulfonic acid salt (for example methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, isethionic, benzenesulfonic, p-toluenesulfonic or camphorsulfonic acid salt), acetic, malic, fumaric, succinic, citric, tartaric, benzoic, gluconic, lactic, mandelic, mucic, pamoic, pantothenic, oxalic and maleic acid salt; and an aminoacid salt such as ornithinic, glutamic and aspartic acid salt. The acid addition salt may be a mono- or di-acid addition salt. A preferred salt is a di-hydrohalogenic, di-sulphuric, di-phosphoric or di-organic acid salt. A most preferred salt is a di-hydrochloric acid salt.

P is a protected ketone functionality. Suitable protecting groups are commonly known in the art, for example from Chapter 4 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

Preferably the protected ketone functionality P is an acyclic ketal or derivative **1q**, a cyclic ketal or derivative **1r**, **1s** or **1t**, or a hydrazone or oxime **1u**, as shown in Figure 4. More preferably P is a cyclic ketal **1r**, most preferably P is a monoethyleneketal **1**, as shown in Figures 2 and 3.

R^1, R^2 and R^3 can be any atom or group. Preferably R^1 and R^2 are not amine protecting groups. Amine protecting groups are commonly known in the art, for example from Chapter 7 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991). Most preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton. Such an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, does not encompass carbonyl -CO-R groups, wherein R is any atom or group.

Optionally R^1, R^2 and R^3 are independently hydrogen or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

Optionally R^1, R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-R^4$-O-R^5, $-R^4$-S-R^5, $-R^4$-SO-R^5, $-R^4$-SO_2-R^5, $-R^4$-N$(R^5)_2$, $-R^4$-Si$(R^5)_3$, $-R^4$-CO-R^5, $-R^4$-CO-OR^5, $-R^4$O-CO-R^5, $-R^4$-CO-N$(R^5)_2$, $-R^4$-NR^5-CO-R^5, $-R^4$-CS-R^5 or $-R^5$, wherein

$-R^4-$ is independently a chemical bond, a C_1-C_{10} alkylene, C_1-C_{10} alkenylene or C_1-C_{10} alkynylene group, and

$-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl.

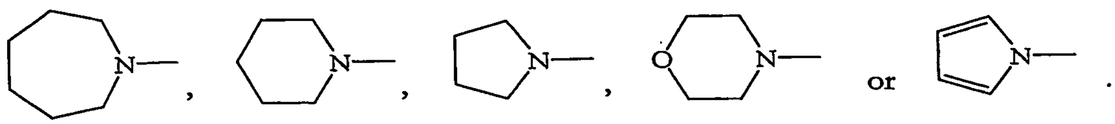
Optionally R^1, R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which does not include any heteroatoms in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-OR^5$, $-SR^5$, -SO-R^5, $-SO_2$-R^5, -N$(R^5)_2$, -Si$(R^5)_3$, -CO-R^5, -CO-OR^5, -O-CO-R^5, -CO-N$(R^5)_2$, -NR^5-CO-R^5, -CS-R^5 or $-R^5$, wherein

$-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl.

Preferably R^1, R^2 and R^3 are independently hydrogen or an unsubstituted alkyl, aryl or heteroaryl group, which does not include any heteroatoms N, O or S in its carbon skeleton. More preferably, R^1, R^2 and R^3 are independently hydrogen or an unsubstituted $C_{1\text{-}10}$ alkyl group. More preferably, R^1, R^2 and R^3 are independently hydrogen or an unsubstituted $C_{1\text{-}6}$ alkyl group. More preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an unsubstituted $C_{1\text{-}6}$ alkyl group, and R^3 is

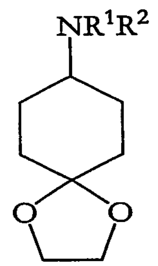
hydrogen. Most preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and R^3 is hydrogen.

Alternatively, R^1 and R^2 can, together with the nitrogen to which they are attached, form a ring. Optionally $-NR^1R^2$ together form an optionally substituted heterocycloalkyl, heterocycloalkenyl or heteroaryl ring. Optionally $-NR^1R^2$ together form

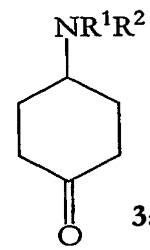


Preferably the reductive amination of step (a) is carried out with $NaCNBH_3$.

A second aspect of the present invention is a 4-amino-cyclohexanone-ethyleneketal **2a** or a 4-amino-cyclohexanone **3a**



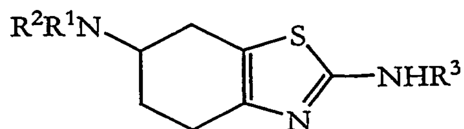
2a



3a

for use in a process of the first aspect of the present invention. R^1 and R^2 are as defined above with reference to the first aspect of the present invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

A third aspect of the present invention is a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a**



5a

or a salt thereof, obtained by a process of the first aspect of the present invention. R^1, R^2 and R^3 are as defined above with reference to the first aspect of the present invention

invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and R^3 is hydrogen. Preferably the compound is a di-hydrochloric acid salt.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** or salts thereof have at least one chiral centre and can therefore exist in the form of various stereoisomers. The present invention embraces all of these stereoisomers and mixtures thereof. Mixtures of these stereoisomers can be resolved by conventional methods, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof of the present invention preferably comprises at least 95% of the (R)- or the (S)-enantiomer, preferably at least 98% of the (R)- or the (S)-enantiomer, and more preferably at least 99% of the (R)- or the (S)-enantiomer. Generally, the (S)-enantiomer is the preferred enantiomer.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof may be used as a medicament, preferably for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fourth aspect of the present invention is a pharmaceutical composition, comprising 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof and a pharmaceutically acceptable carrier or diluent. Preferably the pharmaceutical composition is suitable for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fifth aspect of the present invention is a method of treating a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease, comprising administering a therapeutically effective amount of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof to a subject in need of such treatment.

Brief description of the drawings

Figure 1 is a schematic illustration of the process of the present invention.

Figures 2 and 3 are schematic illustrations of preferred processes of the present invention.

Figure 4 illustrates preferred protected ketone functionalities P.

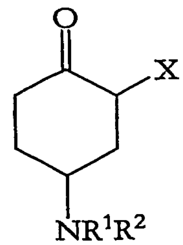
Detailed description of the invention

The inventors have found that processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** are greatly improved by the process outlined in Figure 1, wherein R^1 and R^2 can be any atom or group or, together with the nitrogen to which they are attached, form a ring, and wherein R^3 can be any atom or group. R^1, R^2 and R^3 are preferably hydrogen or an unsubstituted alkyl, aryl or heteroaryl group.

The process outlined in Figure 1 is short, utilises a readily available starting material, a protected cyclohexandione **1p**, and does not require any hazardous chemical reagents. Each step of the process is high yielding and affords products of very high purity.

Therefore a first aspect of the current invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** by the process specified in Figure 1.

It has been disclosed in prior art documents WO 02/22590 and WO 02/22591 that, in practice, compounds of formula **5a**, comprising a primary amino or a secondary alkylamino group, cannot be prepared directly from the corresponding ketones **3a**. The process shown in Figure 1, however, illustrates that the process of the current invention does indeed allow a compound **5a** to be prepared from ketones **3a** directly without the requirement of preparing and isolating an α-haloketone of formula 4, where X is a halide such as chloride or bromide, or the requirement of a protecting group on the nitrogen atom of the amine substituent $-NR^1R^2$ of the ketone **3a**.



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Therefore, in a preferred embodiment of the present invention, the α-haloketone of formula 4 is not isolated. Moreover, in a preferred embodiment of the present invention, the nitrogen atom of the amine substituent $-NR^1R^2$ of the ketone **3a** is not protected.

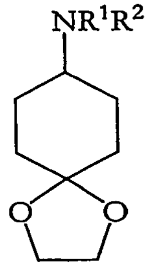
In a preferred embodiment of the first aspect of the invention, cyclohexandione is protected as a cyclohexandione monoethyleneketal **1**, as shown in Figures 2 and 3.

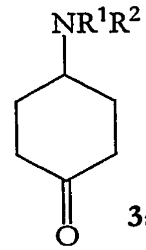
A further preferred embodiment of the first aspect of the invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole **5**, as outlined in Figure 3.

The process outlined in Figure 3 can readily be adapted to afford pramipexole **I** or its salts, for example by resolution of compound **5**. Methods for resolving enantiomers are well known in the art and include, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

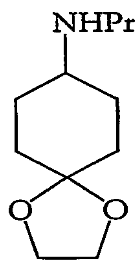
A further aspect of the invention is therefore pramipexole **I** and its salts, when prepared by a process according to the current invention.

Further aspects of the invention include novel compounds of the formula **2a** or **3a**, wherein R^1 and R^2 are as defined above, which are useful intermediates in the synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a**.


2a


3a

Preferred embodiments of these aspects are compounds **2** and **3**, as shown in Figure 3.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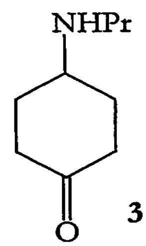
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The process outlined in Figure 3 is an example of a procedure comprising the process of the current invention and detailed procedures for this process are found in the experimental section. Compounds of the current invention are also exemplified in Figure 3 and in the experimental section.

The process of the present invention is short, utilises readily available starting materials and does not involve the use of hazardous or difficult to handle reagents such as bromine, hydrazine or potassium chromate. Each step of the process of the present invention is high yielding and affords products of very high purity. Thus the process is easy to scale up for industrial scale manufacturing. Optionally 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** and salts thereof may be manufactured in batches of 5kg or more, or even 10kg or more.

Experimental procedure

<u>4-*n*-Propylamino-cyclohexanone-ethyleneketal 2</u>

A mixture of *n*-propyl amine (162ml, 1.474mol) in methanol (500ml) was chilled to 0-5°C. To this solution was added methanolic hydrochloric acid (155ml, 44.47%) dropwise over a period of 30 minutes to achieve a pH of 6-7. Cyclohexandione monoethyleneketal **1** (100g, 0.641mol) was charged at 5°C and the reaction was stirred for 15 minutes. Sodium cyanoborohydride (60g, 0.952mol) was added in 15 minutes at 5°C. The pH increased to about 8 and methanolic hydrochloric acid (15ml, 44.47%) was added to bring the pH to 6-7. The reaction was allowed to come to 24-26°C. Stirring was continued for 2 hours. Methanol was distilled off (450ml). Sodium carbonate (95g, 0.896mol) was dissolved in water (850ml) and charged to the reaction mass at ambient temperature in one shot. The reaction mass was extracted with dichloromethane (2500ml). The dichloromethane layers were combined and dried over sodium sulfate (8.5g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product **2** was light yellow viscous oil. The weight of the product **2** obtained was 135g (105.8%); GC purity 97.74%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); 1.5-1.7 (m, 7H, $C\underline{H}_2CH_3$ of *n*Pr and 5H of cyclohexyl ring); 1.75-1.85 (m, 2H, 2H of cyclohexyl ring); 1.95-2.05 (m, 1H, 1H of cyclohexyl ring); 2.75 (t, 2H, $C\underline{H}_2CH_2CH_3$ of *n*Pr); 3.75-3.85 (m, 1H, NHCH); 3.9 (s, 2H, CH_2 of ethylene ketal) and 4.0 (s, 2H, CH_2 of ethylene ketal).
^{13}C NMR (δ ppm): 11.7 (CH_3 of *n*Pr); 21.8 ($\underline{C}H_2CH_3$ of *n*Pr); 28.5 (C-3 and C-5); 33.1 (C-2 and C-6); 48.3 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 55.8 (C-4); 64.5 (C of ethylene ketal); 64.6 (C of ethylene ketal); 108.1 (C-1).

<u>4-*n*-Propylamino-cyclohexanone **3**</u>

4-*N*-propylamino-cyclohexanone-ethyleneketal **2** (134g, 0.673mol) was taken in tetrahydrofuran (268ml) and cooled to 4-6°C. Concentrated hydrochloric acid (178ml, 2.01mol) was diluted with water (2144ml) and the mixture was cooled to 4°C. This diluted hydrochloric acid was added to the reaction mixture at 4-6°C in 15 minutes. The reaction was allowed to come to 24-26°C and stirring was continued for 24 hours. The reaction mass (2750ml) was concentrated to 1800ml at 50°C and 35mbar pressure. Sodium carbonate (148g, 1.4mol) was added to achieve

pH 10. The reaction mixture was extracted with dichloromethane (3670ml). The dichloromethane layers were combined and dried over sodium sulfate (20g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product **3** was yellow viscous oil. The weight of the product **3** obtained was 52.5g (52.84%); GC purity 86.07%.

^1H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 1.6-1.75 (m, 2H, 2H of cyclohexyl ring); 2.05-2.15 (m, 2H, 2H of cyclohexyl ring); 2.2-2.3 (m, 2H, 2H of cyclohexyl ring); 2.4-2.55 (m, 2H, 2H of cyclohexyl ring); 2.55-2.65 (t, 2H, $C\underline{H}_2CH_2CH_3$ of *n*Pr); 2.9-3.0 (m, 1H, NHCH).

^{13}C NMR (δ ppm): 12.3 (CH_3 of *n*Pr); 24.0 ($\underline{C}H_2CH_3$ of *n*Pr); 32.6 (C-3 and C-5); 39.1 (C-2 and C-6); 50.0 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 54.4 (C-4); 211.9 (C-1).

<u>2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole 5</u>

4-*n*-Propylamino-cyclohexanone **3** (5g, 32.26mmol) was charged in absolute ethanol (50ml) at 24-26°C. Iodine (8.5g, 33.5mmol) was added to it under stirring followed by thiourea (5g, 65.7mmol) at 24-26°C. The reaction mass was refluxed for 32 hours. Heating was stopped and the reaction mass was allowed to cool to 24-26°C. It was maintained at that temperature for 20 hours. 2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt crystallized out of the solution. Ethanol (30ml) was distilled out on the rotavapor at 50°C and 100mbar. Acetone (50ml) was added and the solid was filtered. The solid was dried at 40°C and 15mbar. The weight of the product obtained was 8.5g (56%); HPLC purity 94.97%.

^1H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr) 1.6-1.8 (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 2.0 (m, 1H, H-7a); 2.35 (m, 1H, H-7b); 2.7 (m, 3H, H-5a, H-8a, H-8b); 3.1 (m, 3H, H-5b and $C\underline{H}_2CH_2CH_3$ of *n*Pr); 3.7 (m, 1H, NHCH).

^{13}C NMR (δ ppm): 12.0 (CH_3 of *n*Pr); 21.0 ($\underline{C}H_2CH_3$ of *n*Pr); 22.2 (C-7); 25.5 and 26.8 (C-5 and C-8); 48.7 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 54.7 (C-6); 113.0 (C-4); 134 (C-9); 171.2 (C-2).

Mass Spec: M^+ 211 (expected 211).

The 2-amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt formed above (50g, 107.1mmol) was dissolved in water (200ml). The solution was cooled to 4°C and solid sodium hydroxide (50g, 1.25mol) was added in 15 minutes. The reaction was stirred for 1 hour at 24-26°C and the solid that precipitated out was filtered and dried at 40°C and 15mbar. The weight of the product 5 obtained was 17.07g (75.5%); HPLC purity 99.88%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); 1.5-1.6 (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 2.1 (m, 1H, H-7a); 2.3 (m, 1H, H-7b); 2.5-2.6 (m, 5H, H-5a, H-5b, H-8a, H-8b and $C\underline{H}CH_2CH_3$ of *n*Pr); 2.9 (m, 2H, H-6 and $C\underline{H}CH_2CH_3$ of *n*Pr).
^{13}C NMR (δ ppm): 12.0 (CH_3 of *n*Pr); 24.6 ($\underline{C}H_2CH_3$ of *n*Pr); 26.6 (C-7); 30.7 and 30.9 (C-5 and C-8); 50.7 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 56.2 (C-6); 116.0 (C-4); 145 (C-9); 170.4 (C-2).
Mass Spec: M^+ 211 (expected 211).

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope of the invention, which is defined by the following claims.